

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1. (Original) Use of at least one proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of diseases associated with endothelial dysfunction.
2. (Original) Use according to claim 1, wherein the diseases associated with endothelial dysfunction are non-insulin related diseases.
3. (Previously Presented) Use according to claim 1, wherein the endothelial dysfunction is associated with atherosclerosis, in particular coronary sclerosis and coronary artery disease.
4. (Previously Presented) Use according to claim 1, wherein the endothelial dysfunction is associated with heart failure.
5. (Previously Presented) Use according to claim 1, wherein the endothelial dysfunction is associated with diseases selected from the group comprising ischemic diseases such as peripheral arterial occlusive disease, e.g. critical leg ischemia, myocardial infarction and ischemic diseases of organs, e.g. of the kidney, spleen, brain, and lung.
6. (Currently Amended) Use according to claim 1, wherein the proteasome inhibitor is selected from a group comprising:
  - a) naturally occurring proteasome inhibitors comprising: peptide derivatives which have a C-terminal epoxy keton structure,  $\beta$ -lacton-derivatives, aclacinomycin A, lactacystin, clastolactacystein;

- b) synthetic proteasome inhibitors comprising:  
modified peptide aldehydes such as N-carbobenzoxy-L-leucinyl-L-leucinyl-L-leucinal (also referred to as MG132 or zLLL), or the boric acid derivative of MG232, N-carbobenzoxy-Leu-Nva-H (also referred to as MG115), N-acetyl-L-leucinyl-L-leucinyl-L-norleucinal (also referred to as LLnL), N-carbobenzoxy-Ile-Glu(OBut)-Ala-Leu-H (also referred to as PS1) [SEQ ID NO: 1];
- c) peptides comprising:  
an  $\alpha,\beta$ -epoxyketone-structure, vinyl-sulfones such as, carbobenzoxy-L-leucinyl-L-leucinyl-L-leucin-vinyl-sulfon or, 4-hydroxy-5-iodo-3-nitrophenylacetyl-L-leucinyl-L-leucinyl-L-leucin-vinyl-sulfon (NLVS);
- d) Glyoxal- or boric acid residues such as: pyrazyl-CONH(CHPhe)CONH(CHisobutyl)B(OH)<sub>2</sub> and dipeptidyl-boric-acid derivatives;
- e) Pinacol-esters such as: benzyloxycarbonyl(Cbz)-Leu-leuboro-Leu-pinacol-ester.

7. (Currently Amended) Use according to claim 1, wherein the proteasome inhibitor is selected from a group comprising PS-314 as a peptidyl-boric-acid derivative which is N-pyrazinecarbonyl-L-phenylalanin-L-leucin- boric acid (C<sub>19</sub>H<sub>25</sub>BN<sub>4</sub>O<sub>4</sub>); PS-519 as a  $\beta$ -lacton- and a lactacystin-derivative which is 1R-[1S, 4R, 5S] -1-(1-Hydroxy-2methylpropyl)-4-propyl-6-oxa-2azabicyclo[3.2.0]heptane-3,7-dione (C<sub>12</sub>H<sub>19</sub>NO<sub>4</sub>); PS-273 (morpholin-CONH-(CH-naphthyl)-CONH-(CH-isobutyl)-B(OH)<sub>2</sub>) and its enantiomer; PS-293; PS-296 (8-quinolyl-sulfonyl-CONH-(CH-naphthyl)-CONH(-CH-isobutyl)-B(OH)<sub>2</sub>); PS-303 (NH<sub>2</sub>(CH-naphthyl)-CONH-(CH-isobutyl)-B(OH)<sub>2</sub>; PS-321 as (morpholin-CONH-(CH-naphthyl)-CONH-(CH-phenylalanin)-B(OH)<sub>2</sub>); PS-334

(CH<sub>3</sub>-NH-(CH-naphthyl-CONH-(CH-isobutyl)-B(OH)<sub>2</sub>); PS-325 (2-quinol-CONH-(CH-homo-phenylalanin)-CONH-(CH-isobutyl)-B(OH)<sub>2</sub>; PS-352 (phenylalanin-CH<sub>2</sub>-CH<sub>2</sub>-CONH-(CH-isobutyl)-B(OH)<sub>2</sub>; PS-383 (pyridyl-CONH-(CH<sub>p</sub>F-phenylalanin)-CONH-(CH-isobutyl)-B(OH)<sub>2</sub>); PS-341; and PS-1 Z-Ile-Glu(OtBu)-Ala-Leu-CHO [SEQ ID NO: 1]; PS-2 [Benzoyloxycarbonyl]-Leu-Leu-phenylalaninal or Z-LLF-CHO or Z-Leu-Leu-Phe-CHO PS-1; PS-519 as a  $\beta$ -lacton- and a lactacystin-derivative which is 1R-[1S, 4R, 5S]-1-(1-Hydroxy-2methylpropyl)-4-propyl-6-oxa-2azabicyclo[3.2.0]heptane-3,7-dione (C<sub>12</sub>H<sub>19</sub>NO<sub>4</sub>); epoxomicin (C<sub>28</sub>H<sub>86</sub>N<sub>4</sub>O<sub>7</sub>) and eponemycin (C<sub>20</sub>H<sub>36</sub>N<sub>2</sub>O<sub>5</sub>).

8. (Previously Presented) Use according to claim 1, wherein the proteasome inhibitor is selected from a group comprising a peptide aldehyde, a peptide boronate, a peptide vinylsulfone, a peptide epoxyketone, a lactacystin, a peptide  $\alpha$ -ketonaldehyde, an  $\alpha$ -ketoamide, an indanonpeptide, a polyalkylenaldehyde, a polyphenol such as cathechin-3-gallate.

9. (Currently Amended) Use according to claim 1, wherein the proteasome inhibitor is selected from a group comprising Z-Leu-Leu-Leu-al (MG132), Z-Ile-Glu(OtBu)-Ala-Leu-al (PS-1) [SEQ ID NO: 1], CEP1612, pyrazylcarbonyl-Phe-Leu-boronate (PS-341), dansyl-Phe-Leu-boronate (DFLB), morpholinonaphthylalanin-Leu-boronate (MG273), NIP-Leu<sub>3</sub>-vinylsulfone (NLVS), Tyr-Leu<sub>3</sub>-VS [SEQ ID NO: 2], NIP-Leu-Leu-Asn-VS, Ada-Tyr-Ahx<sub>3</sub>-Leu<sub>3</sub>-VS [SEQ ID NO: 3], Ada-Lys(bio)-Ahx<sub>3</sub>-Leu<sub>3</sub>-VS [SEQ ID NO: 4], Ac(Me)-Ile-Ile-Thr-Leu-EX (epoxomicin) [SEQ ID NO: 5], dihydroeponemycin, lactacystin, clasto-lactacystin-beta-lacton (omuralid), PS-519, Ac-Leu-Leu-Nle-al (ALLN), 3,4-dichloroisocoumarin (DCI), 4-(2-aminoethyl)-bezolsulfonylfluorid (pefablock SC), TMC-95-A, gliotoxin, (-)epigallocatechin-3-gallate (EGCG), ritonavir, lovastatin, aclacinomicin A (aclarubicin), cyclosporin, wherein Z represents benzyl oxycarbonyl, all represents aldehyde, VS represents vinylsulfone, NIP represents 3-nitro-4-hydroxy-5-iodophenylacetate, and bio represents biotin.

10. (Previously Presented) Use according to claim 1, wherein the proteasome inhibitor interferes with gene expression of at least one component of the proteasome complex.
11. (Original) Use according to claim 10, wherein the proteasome inhibitor interfering with proteasomal gene expression is selected from a group comprising antisense RNA, double stranded RNA and oligonucleotides hybridising with a DNA sequence encoding at least one component of the proteasome complex.
12. (Previously Presented) Use according to claim 10, wherein the proteasome inhibitor interfering with proteasomal gene expression is selected from a group comprising a knock out construct.
13. (Original) Use of at least one proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of a disease, wherein the proteasome inhibitor dose provided to a patient in need is in the nmol range.
14. (Original) Use according to claim 13, wherein the disease is associated with endothelial dysfunction.
15. (Previously Presented) Use according to claim 13, wherein the disease associated with endothelial dysfunction is a non-insulin related disease.
16. (Previously Presented) Use according to claim 13, wherein the endothelial dysfunction is associated with atherosclerosis, in particular coronary sclerosis and coronary artery disease.
17. (Previously Presented) Use according to claim 13, wherein the endothelial dysfunction is associated with heart failure.

18. (Previously Presented) Use according to claim 13, wherein the endothelial dysfunction is associated with diseases selected from the group comprising ischemic diseases such as peripheral arterial occlusive disease, e.g. critical leg ischemia, myocardial infarction and ischemic diseases of organs, e.g. of the kidney, spleen, brain, and lung.

19. (Currently Amended) Use according to claim 13, wherein the proteasome inhibitor is selected from a group comprising:

- a) naturally occurring proteasome inhibitors comprising:  
peptide derivatives which have a C-terminal epoxy keton structure,  $\beta$ -lacton-derivatives, aclacinomycin A, lactacystin, clastolactacystein;
- b) synthetic proteasome inhibitors comprising:  
modified peptide aldehydes such as N-carbobenzoxy-L-leucinyl-L-leucinyl-L-leucinal (also referred to as MG132 or zLLL), or the boric acid derivative of MG232, N-carbobenzoxy-Leu-Nva-H (also referred to as MG115), N-acetyl-L-leucinyl-L-leucinyl-L-norleucinal (also referred to as LLnL), N-carbobenzoxy-Ile-Glu(OBut)-Ala-Leu-H (also referred to as PS-1) [SEQ ID NO: 1];
- c) peptides comprising:  
an  $\alpha,\beta$ -epoxyketone-structure, vinyl-sulfones such as, carbobenzoxy-L-leucinyl-L-leucinyl-L-leucin-vinyl-sulfon or, 4-hydroxy-5-iodo-3-nitrophenylacetyl-L-leucinyl-L-leucinyl-L-leucin-vinyl-sulfon (NLVS);
- d) Glyoxal- or boric acid residues such as: pyrazyl-CONH(CHPhe)CONH(CHisobutyl)B(OH)<sub>2</sub> and dipeptidyl-boric-acid derivatives;

e) Pinacol-esters such as: benzyloxycarbonyl(Cbz)-Leu-leuboro-Leu-pinacol-ester.

20. (Currently Amended) Use according to claim 13, wherein the proteasome inhibitor is selected from a group comprising PS-314 as a peptidyl-boric-acid derivative which is N-pyrazinecarbonyl-L-phenylalanin-L-leucin- boric acid ( $C_{19}H_{25}BN_4O_4$ ); PS-519 as a  $\beta$ -lacton- and a lactacystin-derivative which is 1R-[1S, 4R, 5S]-1-(1-Hydroxy-2methylpropyl)-4-propyl-6-oxa-2azabicyclo[3.2.0]heptane-3,7-dione ( $C_{12}H_{19}NO_4$ ); PS-273 (morpholin-CONH-(CH-naphthyl)-CONH-(CH-isobutyl)-B(OH)<sub>2</sub>) and its enantiomer; PS-293; PS-296 (8-quinolyl-sulfonyl-CONH-(CH-naphthyl)-CONH(-CH-isobutyl)-B(OH)<sub>2</sub>); PS-303 ( $NH_2(CH\text{-naphthyl})\text{-CONH-(CH-isobutyl)\text{-B(OH)}}_2$ ; PS-321 as (morpholin-CONH-(CH-naphthyl)-CONH-(CH-phenylalanin)-B(OH)<sub>2</sub>); PS-334 ( $CH_3\text{-NH-(CH-naphthyl)\text{-CONH-(CH-isobutyl)\text{-B(OH)}}_2$ ); PS-325 (2-quinol-CONH-(CH-homo-phenylalanin)-CONH-(CH-isobutyl)-B(OH)<sub>2</sub>; PS-352 (phenylalanin- $CH_2\text{-CH}_2\text{-CONH-(CH-isobutyl)\text{-B(OH)}}_2$ ; PS-383 (pyridyl-CONH-(CH<sub>p</sub>F-phenylalanin)-CONH-(CH-isobutyl)-B(OH)<sub>2</sub>); PS-341; and PS-1 Z-Ile-Glu(OtBu)-Ala-Leu-CHO [SEQ ID NO: 1]; PS-2 [Benzylloxycarbonyl]-Leu-Leu-phenylalaninal or Z-LLF-CHO or Z-Leu-Leu-Phe-CHO PS-1; PS-519 as a  $\beta$ -lacton- and a lactacystin-derivative which is 1R-[1S, 4R, 5S]-1-(1-Hydroxy-2methylpropyl)-4-propyl-6-oxa-2azabicyclo[3.2.0]heptane-3,7-dione ( $C_{12}H_{19}NO_4$ ); epoxomicin ( $C_{28}H_{86}N_4O_7$ ) and eponemycin ( $C_{20}H_{36}N_2O_5$ ).

21. (Previously Presented) Use according to claim 13, wherein the proteasome inhibitor is selected from a group comprising a peptide aldehyde, a peptide boronate, a peptide vinylsulfone, a peptide epoxyketone, a lactacystin, a peptide  $\alpha$ -ketonaldehyde, an  $\alpha$ -ketoamide, an indanonpeptide, a polyalkylenaldehyde, a polyphenol such as cathechin-3-gallate.

22. (Currently Amended) Use according to claim 13, wherein the proteasome inhibitor is selected from a group comprising Z-Leu-Leu-Leu-al (MG132), Z-

Ile-Glu(OtBu)-Ala-Leu-al (PS-1) [SEQ ID NO: 1], CEP1612, pyrazylcarbonyl-Phe-Leu-boronate (PS-341), dansyl-Phe-Leu-boronate (DFLB), morpholinonaphthylalanin-Leu-boronate (MG273), NIP-Leu<sub>3</sub>-vinylsulfone (NLVS), Tyr-Leu<sub>3</sub>-VS [SEQ ID NO: 2], NIP-Leu-Leu-Asn-VS, Ada-Tyr-Ahx<sub>3</sub>-Leu<sub>3</sub>-VS [SEQ ID NO: 3], Ada-Lys(bio)-Ahx<sub>3</sub>-Leu<sub>3</sub>-VS [SEQ ID NO: 4], Ac(Me)-Ile-Ile-Thr-Leu-EX (epoxomicin) [SEQ ID NO: 5], dihydroeponemycin, lactacystin, clasto-lactacystin-beta-lacton (omuralid), PS-519, Ac-Leu-Leu-Nle-al (ALLN), 3,4-dichloroisocoumarin (DCI), 4-(2-aminoethyl)-bezolsulfonylfluorid (pefablock SC), TMC-95-A, gliotoxin, (-)epigallocatechin-3-gallate (EGCG), ritonavir, lovastatin, aclacinomicin A (aclarubicin), cyclosporin, wherein Z represents benzyl oxycarbonyl, al represents aldehyde, VS represents vinylsulfone, NIP represents 3-nitro-4-hydroxy-5-iodophenylacetate, and bio represents biotin.

23. (Previously Presented) Use according to claim 13, wherein the proteasome inhibitor is MG132.
24. (Previously Presented) Use according to claim 13, wherein the proteasome inhibitor interferes with gene expression of at least one component of the proteasome complex.
25. (Previously Presented) Use according to claim 13, wherein the proteasome inhibitor interfering with proteasomal gene expression is selected from a group comprising antisense RNA, double stranded RNA and oligonucleotides hybridising with a DNA sequence encoding at least one component of the proteasome complex.
26. (Previously Presented) Use according to claim 13, wherein the proteasome inhibitor interfering with proteasomal gene expression is selected from a group comprising a knock out construct.